



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07D 311/00	A2	(11) International Publication Number: WO 98/21197 (43) International Publication Date: 22 May 1998 (22.05.98)
(21) International Application Number: PCT/EP97/06227 (22) International Filing Date: 10 November 1997 (10.11.97) (30) Priority Data: 96118037.9 11 November 1996 (11.11.96) EP (34) Countries for which the regional or international application was filed: DE et al. (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 24, CH-4070 Basle (CH). (72) Inventors: BAAK, Marcel; Ebenrainweg 7, CH-4450 Sissach (CH). BONRATH, Werner; Haslacherstrasse 140, D-79115 Freiburg (DE). PAULING, Horst; Ruchholzstrasse 39, CH-4103 Bottmingen (CH). (74) Agent: KELLENBERGER, Marcus; Grenzacherstrasse 124, CH-4070 Basle (CH).		(81) Designated States: CN, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: PROCESS FOR MANUFACTURING d,l- α -TOCOPHEROL (57) Abstract A process for the manufacture of d,l- α -tocopherol by the catalyzed condensation of trimethylhydroquinone with isophytol comprises carrying out the condensation in the presence of bis-(trifluoromethylsulphonyl)amine [HN(SO ₂ CF ₃) ₂] or a metal salt thereof of the formula Met [N(SO ₂ CF ₃) ₂] _n (I), wherein Met signifies a metal atom selected from the group of lithium, boron, magnesium, aluminium, silicon, scandium, titanium, vanadium, manganese, iron, cobalt, nickel, copper, zinc, yttrium, zirconium, rhodium, palladium, silver, tin, lanthanum, cerium, neodymium, praseodymium, europium, dysprosium, ytterbium, hafnium, platinum and gold and n signifies the corresponding valency (1, 2, 3 or 4) of the metal atom Met, as the catalyst or of a combination of a metal salt of formula (I) and a strong Bronsted acid as the catalyst system in an organic solvent. The product of the process is the most active member of the vitamin E group.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Process for Manufacturing d,l- α -Tocopherol

The present invention is concerned with a novel process for the manufacture of d,l- α -tocopherol by the catalyzed condensation of
5 trimethylhydroquinone with isophytol. As is known, d,l- α -tocopherol is a diastereomer mixture of 2,5,7,8-tetramethyl-2-(4',8',12'-trimethyl-tridecyl)-6-chromanol (α -tocopherol), which is the most active and industrially most important member of the vitamin E group.

10 Various processes for the manufacture of d,l- α -tocopherol by the condensation of trimethylhydroquinone (TMHQ) with isophytol (IP) in the presence of a catalyst or catalyst system have already been described. These processes go back to the work of Karrer et al., Bergel et al. as well as Smith et al. [see *Helv. Chim. Acta* 21, 520 et seq. (1938), *Nature* 142, 36 et seq. (1938)
15 and, respectively, *Science* 88, 37 et seq. (1938) and *J. Am. Chem. Soc.* 61, 2615 et seq. (1939)]. While Karrer et al. carried out the synthesis of d,l- α -tocopherol from TMHQ and phytol bromide in the presence of anhydrous zinc chloride (a Lewis acid), not only Bergel et al. but also Smith et al. used TMHQ and phytol as starting materials. In the following years mainly
20 modifications, e.g. alternative solvents and Lewis acids, were developed. From the work of Karrer et al. there was developed in the year 1941 a technically interesting process for the manufacture of d,l- α -tocopherol, which was based on the condensation of TMHQ with IP in the presence of the catalyst system zinc chloride/hydrochloric acid (US Patent 2 411 969).
25 Later publications, e.g. Japanese Patent Publications (Kokai) 54380/1985, 64977/1985 and 226979/1987 [see *Chemical Abstracts (C.A.)* 103, 123731s (1985), *C.A.* 103, 104799d (1985) and, respectively, *C.A.* 110, 39217r (1989)], describe this condensation in the presence of zinc and zinc chloride (ZnCl_2) and a protonic acid, such as a hydrohalic acid, e.g. hydrochloric acid (HCl),
30 trichloroacetic acid, acetic acid and the like, especially ZnCl_2/HCl , as the catalyst system.

The manufacture of d,l- α -tocopherol by the reaction of TMHQ with phytyl chloride or isophytol in the presence of boron trifluoride (BF_3) or its
35 etherate ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) is described in German Offenlegungsschriften (DOS) 960720 and 1015446 as well as in US Patents 3 444 123 and 4 634 781. However, boron trifluoride has corrosive properties.

Also, the condensation of TMHQ with IP or phytol, which has been treated with ammonia or amines, in the presence of ZnCl_2/HCl or a Lewis acid, e.g. BF_3 or aluminium trichloride (AlCl_3), and hydrochloric acid as the catalyst system has been described in the patent literature, e.g. in DOS 2 606 830, US Patent 4 634 781 and European Patent Publication (EP) 100471. Again corrosion problems occur.

A further interesting method for the manufacture of d,l- α -tocopherol from TMHQ and IP comprises using isolated TMHQ- AlCl_3 complexes (DOS 1909164). This process variant avoids to a large extent the formation of undesired byproducts because it involves mild reaction conditions. The yield of d,l- α -tocopherol is given as 77% based on IP. The use of solvent mixtures, such as e.g. methylene chloride/nitromethane, is disadvantageous.

Using the reaction described in the literature of TMHQ with IP in the presence of ZnCl_2 in combination with acids such as trichloroacetic acid, acetic acid or acidic salts, such as sodium hydrogen sulphate, d,l- α -tocopherol cannot be manufactured in the required purity (about 85%) (see, for example, DOS 1909164).

A further application of ZnCl_2 - with the addition of bromine - in the condensation of TMHQ with IP is disclosed in Czechoslovakian Patent 205952.

A further method for the condensation of TMHQ with IP to d,l- α -tocopherol is effected using a mixture of silicic acid and aluminium oxide pre-treated with protonic acids (see DOS 2404621). This method gives d,l- α -tocopherol in 90% yield; the required excess of IP (based on TMHQ) is, however, disadvantageous.

The manufacture of d,l- α -tocopherol by the condensation of TMHQ with IP using ion exchangers in combination with metal ions (Zn^{2+} , Sn^{2+} and Sn^{4+}) disclosed in Bull Chem, Soc. Japan 50, 2477 et seq. (1977) gives the product in 70-87.5% yield.

All processes using ZnCl_2 in combination with Bronsted acids as catalyst systems feature as a disadvantage the occurrence of corrosion problems and a potential contamination of the waste water with zinc ions.

The use of ion exchangers (Amberlyst® 15) as the catalyst for the condensation of TMHQ with IP is described in US Patent 3459773. However, the d,l- α -tocopherol could not be obtained in the requisite purity.

5

The manufacture of d,l- α -tocopherol in liquid or super-critical carbon dioxide by the condensation of TMHQ with IP in the presence of ion exchangers takes place according to EP 603 695 in about 85% yield.

10

The condensation in the presence of a catalyst system which consists of iron(II) chloride, metallic iron and hydrogen chloride gas is described in DOS 2160103 and US Patent 3789086. The formation of less byproducts is advantageous compared with the aforementioned process using zinc chloride and hydrochloric acid. However, corrosion problems and chloride

15

contamination are equally disadvantageous. An interesting alternative for the condensation of TMHQ with IP to d,l- α -tocopherol comprises using trifluoroacetic acid (EP 12824). Of advantage in this process are the good recyclization of the acid and the

20

avoidance of hydrochloric acid. Disadvantageous are the facts that trifluoroacetic acid is relatively expensive and suitable materials for a production process are difficult to obtain.

25

The use of heterogeneous silicate-based catalysts (clays; especially zeolites) for the condensation is described in C.A. 100, 22833 (1984) and gives d,l- α -tocopherol in a yield of about 92%.

30

The use of heteropolytungsten acids as catalysts for the condensation of TMHQ with IP has been described for the first time in React. Kinet. Catal. Lett. 47, 59 et seq. (1992). d, l- α -Tocopherol could be obtained in 90% yield with this process using toluene as the solvent. The separation of the catalyst and more precise experimental details, such as e.g. the dosage of the isophytol, are, however, not described in this literature reference. The excess of IP based on TMHQ is a disadvantage.

35

A further process described in the literature for the synthesis of d,l- α -tocopherol is based on the use of lathanide triflates, such as e.g. scandium trifluoromethanesulphonate. With a 10% excess of IP this process gives yields of 96-98% [EP 658 552; Bull. Chem. Soc. Japan 68, 3569 et seq. (1995)].

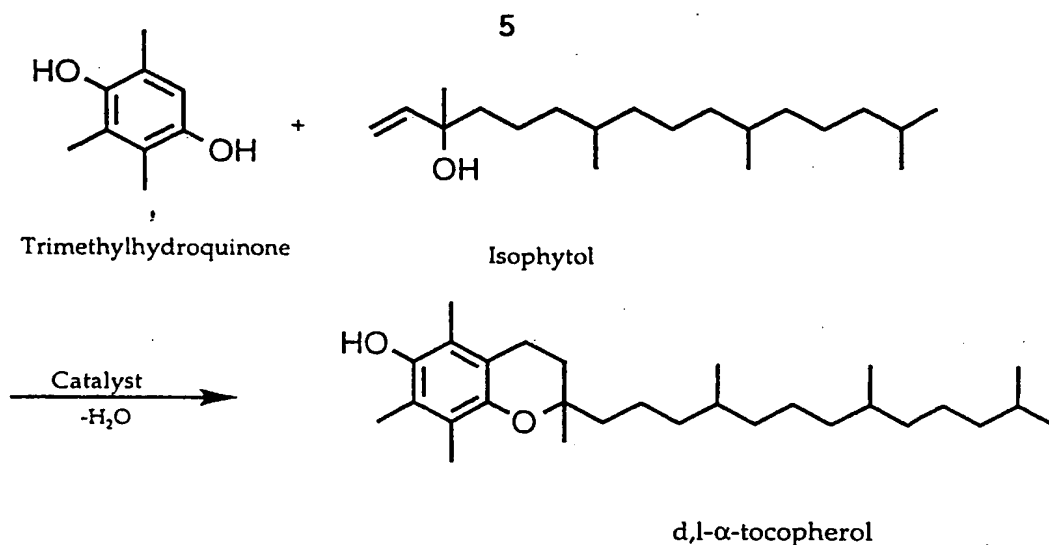
The use of scandium chlorides and other chlorides (yttrium, lanthanum etc.) on a carrier, e.g. bentonite or montmorillonite, as the catalyst for the condensation of TMHQ with IP has as disadvantages the
5 need for a large amount of catalyst and an excess (about 10%) of IP [EP 677 522; Bull. Chem. Soc. Japan 69, 137 et seq. (1996)].

According to EP 694 544 the condensation of TMHQ with IP in isopropyl acetate catalyzed by ZnCl_2/HCl gives d,l- α -tocopherol in yields of
10 98.6% with a purity of 98.6%. Disadvantageous in this process are, in addition to the contamination of the waste water by zinc ions, the large "catalyst amounts" (e.g. 23.3 g of ZnCl_2 for 67 g of product) and the isophytol excess.

15 From the forgoing explanations it will be evident that the previously known processes have considerable disadvantages. Thus, corrosion problems occur in the case of all processes, when boron trifluoride is used toxicity problems with the boron trifluoride adducts also occur and when
20 iron or zinc is used there is a contamination of the waste water with iron or zinc ions which is today no longer acceptable. In the case of some processes the formation of undesired byproducts, e.g. phytyltoluene and chlorophytols, is an especially serious problem.

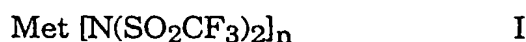
The object of the present invention is to provide a process for the
25 manufacture of d,l- α -tocopherol by the condensation of trimethylhydroquinone with isophytol in the presence of a catalyst which does not have the disadvantages of previously known procedures. In this respect, it is necessary that the catalyst used does not have a corrosive action, is non-toxic, does not contaminate the environment and catalyzes the desired
30 reaction as selectively as possible and in high yields. Furthermore, the catalyst should display its activity already in really only catalytic amounts, and should be readily separable and re-usable several times.

In the scope of the present invention this object is achieved by carrying
35 out the condensation of trimethylhydroquinone with isophytol in the presence of a particular amine catalyst and in an organic solvent. The condensation is effected according to the following Reaction Scheme which is presented conventionally:



in which the catalyst is a particular amine catalyst the nature of which will be explained in more detail below. Moreover, the condensation is carried out in an organic solvent.

The process in accordance with the invention for the manufacture of d,l-α-tocopherol by the catalyzed condensation of trimethylhydroquinone with isophytol comprises carrying out the condensation in the presence of bis-(trifluoromethylsulphonyl)amine [HN(SO₂CF₃)₂] or of a metal salt thereof of the formula



wherein

Met signifies a metal atom selected from the group of lithium, boron, magnesium, aluminium, silicon, scandium, titanium, vanadium, manganese, iron, cobalt, nickel, copper, zinc, yttrium, zirconium, rhodium, palladium, silver, tin, lanthanum, cerium, neodymium, praseodymium, europium, dysprosium, ytterbium, hafnium, platinum and gold

and n signifies the corresponding valency (1, 2, 3 or 4) of the metal atom Met,

as the catalyst or of a combination of a metal salt of formula I and a strong Bronsted acid as the catalyst system in an organic solvent.

Not only bis-(trifluoromethylsulphonyl)amine, but also some of the metal salts of formula I are known compounds [see, for example, EP 364 340, Japanese Patent Publication (Kokai) 246 338/1995, DOS 19533711, Synlett 1996, 171-172, Synlett 1996, 265-266, Chem. Lett. 1995, 307-308 as well as the further
5 literature references mentioned in this state of the art]. The metal salts of formula I which may still not be known can be produced according to methods known per se, namely from the corresponding metal acetates, oxides, hydroxides and alcoholates analogously to known methods. In the case of the aluminium salt and the zinc salt of bis-(trifluoromethyl-
10 sulphonyl)amine (of the formula $\text{Al}[\text{N}(\text{SO}_2\text{CF}_3)_2]_3$ and, respectively, $\text{Zn}[\text{N}(\text{SO}_2\text{CF}_3)_2]_2$), these can also be produced from a corresponding alkylmetal or dialkylmetal hydride, e.g. diethylzinc or triethylaluminium or, respectively, diisobutylaluminium hydride.

15 The metal salts of the bis-(trifluoromethylsulphonyl)amine can be present in monomeric or polymeric form and, accordingly, formula I is intended to embrace all such forms. Further, these catalysts can be used in isolated form or produced in situ.

20 The Bronsted acid present in the catalyst system is an inorganic or organic acid of this type. Sulphuric acid, phosphoric acid and p-toluene-sulphonic acid are examples of Bronsted acids.

Solvents which can be used in the scope of the present invention are
25 aprotic solvents, especially aliphatic and cyclic ketones, e.g. isobutyl methyl ketone and diethyl ketone and, respectively, cyclopentanone and isophorone; aliphatic and cyclic esters, e.g. ethyl acetate, isopropyl acetate and, respectively, γ -butyrolactone; and aromatic hydrocarbons, e.g. toluene and xylene. In the condensation it is advantageous to remove the resulting water
30 by azeotropic distillation.

The condensation is conveniently effected at temperatures between about 80°C and about 150°C, preferably between about 100°C and about 140°C, especially between about 105°C and about 120°C.

35 Furthermore, about equimolar amounts of the two educts trimethylhydroquinone and isophytol are conveniently used. The amount of catalyst is conveniently about 0.08-0.3 mol% in the case of the bis-(trifluoromethylsulphonyl)amine and conveniently about 0.5-4 mol% in the case of a metal

salt of formula I, in each case based on the amount of educt (trimethylhydroquinone or isophytol). Where a catalyst system (combination of a metal salt of formula I and a strong Bronsted acid) is used, the amount of metal salt is conveniently about 0.1-4 mol% and the amount of Bronsted acid is
5 conveniently about 0.01-0.5 mol%, in each case based on the amount of educt.

Furthermore, about 25-100 ml, preferably about 40-50 ml, of organic solvent are conveniently used per 100 mmol of educt.

10 The process in accordance with the invention can be carried out operationally in a very simple manner by adding isophytol dropwise to a suspension of trimethylhydroquinone and catalyst in a solvent. The rate at which the isophytol is added is not critical. Conveniently, isophytol is added dropwise over a period 0.5 to 5 hours. After completion of the isophytol
15 addition and an appropriate subsequent reaction period the working-up is effected by procedures conventionally used in organic chemistry.

The process in accordance with the invention enables the catalyst used to be separated readily and to be re-used several times.

20

Advantages in the use of the catalyst in the process in accordance with the invention are, in addition to high yields of d,l- α -tocopherol, the avoidance of corrosion, the avoidance of waste water contamination with heavy metal ions, the high selectivity as well as the enabled ready separation from
25 unreacted trimethylhydroquinone.

Moreover, it is notable that neither the bis-(trifluoromethylsulphonyl)amine nor a derivative thereof has previously been used for condensation reactions, not to mention for the manufacture of d,l- α -
30 tocopherol. Furthermore, no amines have hitherto been used as catalysts for the condensation of trimethylhydroquinone with isophytol to d,l- α -tocopherol.

The process in accordance with the invention is illustrated by the
35 following Examples:

Example 1

31.4 g (200 mmol) of trimethylhydroquinone (TMHQ; 97%) are suspended in 100 ml of toluene under reflux and under argon as the protective gas in a 500 ml four-necked round flask fitted with a gas inlet tube, stirrer, thermometer, water separator and dosage device. The suspension is treated with 0.7 ml of a solution of 1.37 g of bis-(trifluoromethylsulphonyl)-amine in 10 ml of toluene (containing about 84 mg of catalyst). To this suspension are subsequently added at 140°C (oil bath temperature) 73.02 ml (200 mmol) of isophytol (IP; 96%) at a rate of addition of 2.4 ml per minute (addition time = 30 minutes). Subsequently, the mixture is boiled at 140°C (oil bath temperature) for a further 30 minutes. During the reaction the TMHQ passes into solution, and the internal temperature of the reaction mixture rises from 110°C to 120°C. After completion of the reaction a dark brown solution is obtained. After cooling to room temperature the reaction solution is transferred into a 1 l round flask and concentrated under reduced pressure at 50°C and 20 mbar (2 kPa).

In this manner there are obtained 90% of theory of d,l- α -tocopherol.

Examples 2-36

According to the procedure described in Example 1, equimolar amounts of TMHQ and IP are condensed with each other in the presence of bis(trifluoromethylsulphone)imide or a metal salt thereof of formula I in order to produce d, l- α -tocopherol. The respective variable details of the operation as well as the results are compiled in the following Table in which, inter alia, the catalyst is represented in each case by its chemical formula:

Table

Example No.	Catalyst	Catalyst Amount	mmol TMHQ/IP	Solvent	Solvent amount	d,l- α -Tocopherol Yield
2	HN(SO ₂ CF ₃) ₂	1.37 g	200	Isobutyl methyl ketone	100 ml	92.5%
3	"	"	"	Isopropyl acetate	"	91.7%
4	"	"	"	Ethyl acetate	"	87.2%
5	Mg[N(SO ₂ CF ₃) ₂] ₂	1.17 g	100	Toluene	45 ml	92.6%
6	"	1.25 g	"	Isobutyl methyl ketone	"	75%
7	Al[N(SO ₂ CF ₃) ₂] ₃	1.73 g	"	Toluene	"	78%
8	"	0.56 g	"	"	"	89%
9	Sc[N(SO ₂ CF ₃) ₂] ₃	0.27 g	"	"	"	86.6%
10	V[N(SO ₂ CF ₃) ₂] ₃	1.78 g	"	"	"	76.3%
11	Mn[N(SO ₂ CF ₃) ₂] ₂	1.23 g	"	"	"	92.5%

12	"	"	"	Isobutyl methyl ketone	"	87.9%
13	"	"	"	Isopropyl acetate	"	77.1%
14	$\text{Fe}[\text{N}(\text{SO}_2\text{CF}_3)_2]_2$	0.31-1.23 g	"	Toluene	"	86.2-91.6%
15	$\text{Fe}[\text{N}(\text{SO}_2\text{CF}_3)_2]_3$	1.79 g	"	"	"	85.5%
16	$\text{Co}[\text{N}(\text{SO}_2\text{CF}_3)_2]_2$	1.24 g	"	"	"	87.2%
17	$\text{Ni}[\text{N}(\text{SO}_2\text{CF}_3)_2]_2$	1.25 g	"	"	"	91.3%
18	$\text{Cu}[\text{N}(\text{SO}_2\text{CF}_3)_2]_2$	0.05 g	"	"	"	86%
19	$\text{Zn}[\text{N}(\text{SO}_2\text{CF}_3)_2]_2$	0.07-1.25 g	"	"	"	86-93%
20	"	1.24 g	"	Isobutyl methyl ketone	"	90%
21	$\text{Y}[\text{N}(\text{SO}_2\text{CF}_3)_2]_3$	0.45 g	"	Toluene	"	89.5%
22	$\text{Pd}[\text{N}(\text{SO}_2\text{CF}_3)_2]_2$	1.34 g	"	"	"	80%
23	$\text{Ag}[\text{N}(\text{SO}_2\text{CF}_3)_2]$	1.34 g	"	"	"	82%
24	$\text{Sn}[\text{N}(\text{SO}_2\text{CF}_3)_2]_2$	1.36 g	"	"	"	84.8%
25	$\text{La}[\text{N}(\text{SO}_2\text{CF}_3)_2]_3$	1.96 g	"	"	"	91.1%

26	"	2.00 g	"	Isobutyl methyl ketone	"	92.6%
27	"	"	"	Isopropyl acetate	"	90.3%
28	Ce[N(SO ₂ CF ₃) ₂] ₄	1.96 g	"	Toluene	"	90.2%
29	Nd[N(SO ₂ CF ₃) ₂] ₃	1.97 g	"	"	"	89.5%
30	Pr[N(SO ₂ CF ₃) ₂] ₃	1.96 g	"	"	"	92.8%
31	Eu[N(SO ₂ CF ₃) ₂] ₃	1.99 g	"	"	"	82.7%
32	Dy[N(SO ₂ CF ₃) ₂] ₃	2.00 g	"	"	"	87.5%
33	Yb[N(SO ₂ CF ₃) ₂] ₃	2.03 g	"	"	"	88.6%
34	Hf[N(SO ₂ CF ₃) ₂] ₄	2.60 g	"	"	"	77.5%
35	B[N(SO ₂ CF ₃) ₂] ₃	1.00 g	200	"	100 ml	88.4%
36	Rh ₂ [N(SO ₂ CF ₃) ₂] ₄	1.2 g	"	"	"	88.4%

Example 37

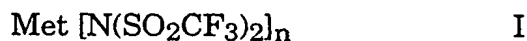
31.8 g (200 mmol) of TMHQ (98.5%) are suspended in 90 ml of toluene under reflux and under argon as the protective gas in a 500 ml four-necked
5 round flask fitted with a gas inlet tube, stirrer, thermometer, water separator and dosage device. The suspension is treated with 1.15 g of bis-(trifluoromethylsulphonyl)amine lithium salt and 80 mg of p-toluene-sulphonic acid. The further procedure is carried out as described in
Example 1.

10

In this manner there are obtained 92% of theory of d,l- α -tocopherol.

Claims

1. A process for the manufacture of d,l- α -tocopherol by the catalyzed condensation of trimethylhydroquinone with isophytol, which process
5 comprises carrying out the condensation in the presence of bis-(trifluoromethylsulphonyl)amine $[\text{HN}(\text{SO}_2\text{CF}_3)_2]$ or a metal salt thereof of the formula



10

wherein

Met signifies a metal atom selected from the group of lithium, boron, magnesium, aluminium, silicon, scandium, titanium, vanadium, manganese, iron, cobalt, nickel, copper, zinc, yttrium, zirconium,
15 rhodium, palladium, silver, tin, lanthanum, cerium, neodymium, praseodymium, europium, dysprosium, ytterbium, hafnium, platinum and gold

and n signifies the corresponding valency (1,2,3 or 4) of the metal atom

20 Met,
as the catalyst or of a combination of a metal salt of formula I and a strong acid as the catalyst system in an organic solvent.

2. A process according to claim 1, wherein an aprotic solvent,
25 especially an aliphatic or cyclic ketone, an aliphatic or cyclic ester, or an aromatic hydrocarbon, is used as the organic solvent.

3. A process according to claim 2, wherein the solvent is isobutyl methyl ketone, ethyl acetate, isopropyl acetate or toluene.

30

4. A process according to any one of claims 1 to 3, wherein the amount of bis-(trifluoromethylsulphonyl)amine used as the catalyst is about 0.08-0.3 mol% and the amount of catalyst of formula I used is about 0.5-4 mol%, in each case based on the amount of trimethylhydroquinone or isophytol.

35

5. A process according to any one of claims 1 to 4, wherein a catalyst system is used in which the amount of metal salt of formula I is about 0.1-4 mol% and the amount of Bronsted acid is about 0.01-0.5 mol%, in each case based on the amount of educt.

6. A process according to any one of claims 1 to 5, wherein about 25-100 ml, preferably about 40-50 ml, of organic solvent are used per 100 mmol of trimethylhydroquinone or isophytol.

5

7. A process according to any one of claims 1 to 6, wherein the condensation is effected at temperatures between about 80°C and about 150°C, preferably between about 100°C and about 140°C, especially between about 105°C and about 120°C.

10

8. A process according to any one of claims 1 to 7, wherein isophytol is added dropwise to a suspension of trimethylhydroquinone and catalyst in a solvent.

15



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 311/72, 311/20	A3	(11) International Publication Number: WO 98/21197 (43) International Publication Date: 22 May 1998 (22.05.98)
(21) International Application Number: PCT/EP97/06227 (22) International Filing Date: 10 November 1997 (10.11.97) (30) Priority Data: 96118037.9 11 November 1996 (11.11.96) EP (34) Countries for which the regional or international application was filed: DE et al. (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 24, CH-4070 Basle (CH). (72) Inventors: BAAK, Marcel; Ebenrainweg 7, CH-4450 Sissach (CH). BONRATH, Werner; Haslacherstrasse 140, D-79115 Freiburg (DE). PAULING, Horst; Ruchholzstrasse 39, CH-4103 Bottmingen (CH). (74) Agent: KELLENBERGER, Marcus; Grenzacherstrasse 124, CH-4070 Basle (CH).		(81) Designated States: CN, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 23 July 1998 (23.07.98)
(54) Title: PROCESS FOR MANUFACTURING d,l- α -TOCOPHEROL (57) Abstract <p>A process for the manufacture of d,l-α-tocopherol by the catalyzed condensation of trimethylhydroquinone with isophytol comprises carrying out the condensation in the presence of bis-(trifluoromethylsulphonyl)amine [HN(SO₂CF₃)₂] or a metal salt thereof of the formula Met [N(SO₂CF₃)₂]_n (I), wherein Met signifies a metal atom selected from the group of lithium, boron, magnesium, aluminium, silicon, scandium, titanium, vanadium, manganese, iron, cobalt, nickel, copper, zinc, yttrium, zirconium, rhodium, palladium, silver, tin, lanthanum, cerium, neodymium, praseodymium, europium, dysprosium, ytterbium, hafnium, platinum and gold and n signifies the corresponding valency (1, 2, 3 or 4) of the metal atom Met, as the catalyst or of a combination of a metal salt of formula (I) and a strong Bronsted acid as the catalyst system in an organic solvent. The product of the process is the most active member of the vitamin E group.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/06227

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D311/72 C07D311/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. ISHIHARA ET AL.: SYNLETT, no. 11, November 1996, pages 1045-6, XP002064088 see page 1045, left-hand column, scheme 1 to right-hand column, table 2 ---	1-3
A	M. MATSUI ET AL.: BULL. CHEM. SOC. JPN., vol. 68, 1995, pages 3569-71, XP002064089 cited in the application ---	1
A	EP 0 658 552 A (EISAI CO., LTD.) 21 June 1995 cited in the application see claims 1-3 --- -/-	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* & * document member of the same patent family

Date of the actual completion of the international search

6 May 1998

Date of mailing of the international search report

25.05.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/06227

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	EP 0 782 993 A (F. HOFFMANN-LA ROCHE AG) 9 July 1997 see claims 1,3-5 ---	1-3
A	EP 0 364 340 A (SOCIETE NATIONALE ELF AQUITAINE) 18 April 1990 cited in the application see examples ---	1
A	DE 195 33 711 A (CENTRAL GLASS CO., LTD.) 14 March 1996 cited in the application see examples ---	1
A	PATENT ABSTRACTS OF JAPAN vol. 96, no. 1, 31 January 1996 & JP 07 246338 A (CENTRAL GLASS CO LTD), 26 September 1995, cited in the application see abstract ---	1
A	H. KOBAYASHI ET AL.: CHEMISTRY LETTERS, 1995, pages 307-8, XP002064090 cited in the application see abstract; tables 1,2 ---	1
A	K. MIKAMI ET AL.: SYNLETT, February 1996, pages 171-2, XP002064091 cited in the application see abstract; tables 1,2 ---	1
A	K. ISHIHARA ET AL.: SYNLETT, March 1996, pages 265-6, XP002064092 cited in the application see page 265, left-hand column, compound 1 see abstract -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/06227

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 658552 A	21-06-95	JP 7224054 A	22-08-95
		CA 2137481 A	15-06-95
		CN 1108254 A	13-09-95
		US 5532387 A	02-07-96
EP 782993 A	09-07-97	JP 9194472 A	29-07-97
EP 364340 A	18-04-90	FR 2637284 A	06-04-90
		CA 2000142 A	05-04-90
		WO 9003968 A	19-04-90
		JP 3501860 T	25-04-91
		US 5256821 A	26-10-93
DE 19533711 A	14-03-96	JP 8081436 A	26-03-96
		FR 2724380 A	15-03-96
		US 5723664 A	03-03-98